Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Tshilolo L, Tomlinson G, Williams TN, et al. Hydroxyurea for children with sickle cell anemia in sub-Saharan Africa. N Engl J Med 2019;380:121-31. DOI: 10.1056/NEJMoa1813598

Realizing Effectiveness across Continents with Hydroxyurea (REACH)

SUPPLEMENTARY APPENDIX

REACH Trial Investigator teams and key contributors

Hospital Pediátrico David Bernardino, Luanda, Angola: Brígida Santos, Luis Bernardino, José Luis Reis da Fonseca, Lourenco Nassesa, Darío Adão de Oliveira André, Leydma Cuhna, Afonso Firmino Bengui, and Vysolela de Oliveira

Centre Hospitalier Monkole, Kinshasa, Democratic Republic of Congo: Léon Tshilolo, Robert Kitenge, Thierry Aberi, Nancy Madingo, Merveille Mbombo, Didier Mbuyi, Patrick Ngoy, Frank Nzengu, Gisèle Kazadi, Joddy Mafema, Guyslain Tshuyi, Yves Mukaba, Landry Kipepe, and Merveille Mbombo

KEMRI Wellcome Trust Research Program, Kilifi, Kenya: Thomas N. Williams, George Mochamah, Alex Macharia, Gideon Nyutu, Jimmy Shangala, Ruth Mwarabu, Metrine Tendwa, Emmanuel Mabibo, Julius Ngowa, Johnstone Makale, Esther Kivaya, Jacob Golijo, Monica Mwikamba, and Kathryn Maitland

Mbale Clinical Research Institute, Mbale, Uganda: Peter Olupot-Olupot, Ham Wabwire, Erayu Godfrey Bonface, Akado Clare, Alex Sande, Felix Opio, and Florence Masambu

Consultants and Supporting Staff: George Tomlinson, University of Toronto, Toronto, Canada; Banu Aygun, Cohen Children's Medical Center, New Hyde Park, New York

Data Management Center, Division of Hematology, Department of Pediatrics, Cincinnati Children's Hospital, USA: Teresa S. Latham, Justin McAdams, Sophie Perier, Jan Englehart, Elizabeth McGann, and John Boesing

Medical Coordinating Center, Division of Hematology, Department of Pediatrics, Cincinnati Children's Hospital, USA: Russell E. Ware, Patrick T. McGann, Adam Lane, Susan E. Stuber, Thad Howard, and Kathryn McElhinney

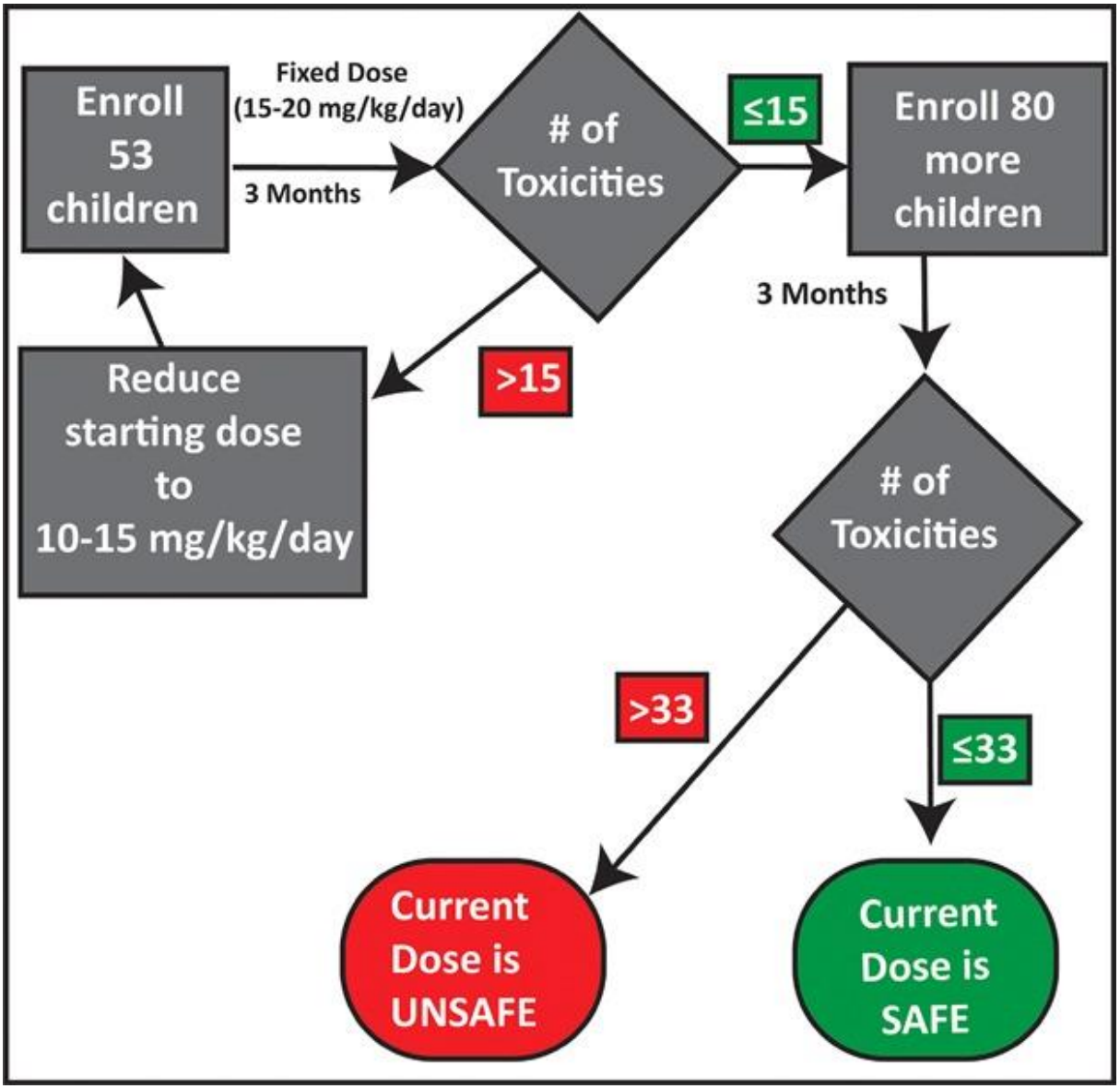

Figure S1. Two-Stage Study Design (from Reference 16)

A study drug shortage occurred in early 2016 due to delays in shipping to the clinical sites. Three sites (02, 03 and 04) had temporary drug shortages that affected dispensing drug. Analysis of the shortage indicated that drug stoppages constituted a small fraction of total follow-up time, and almost all occurred after the 3-month primary safety assessment.

		Site 01 HPDB Luanda, Angola	Site 02 Monkole Kinshasa, DRC	Site 03 KEMRI Kilifi, Kenya	Site 04 MMRH Mbale, Uganda
Study Participants Affected (%)	Dose Adjustment	0%	0%	15%	0%
	Dose Adjustment and Stop	0%	12%	16%	1%
	Drug Stop	0%	70%	24%	8%
Duration of Drug Stop (Average)		N/A	58 days	7 days	23 days

Table S1. Drug shortage

Dose-Limiting Toxicities in the first 90 days of study treatment for the first 133 study participants enrolled at each clinical trial site constitutes the primary safety end-point, with a pre-defined safety margin at each site of ≤33 toxicities. Published data guided an expected (20%) and allowable (30%) toxicity rate.

	Dose-Limiting Toxicities (Participants Affected/Total)	Participants Affected (%)	95% CI
Angola	9/133	6.8	3.6 – 12.4 %
DRC	6/133	4.5	2.1 – 9.5 %
Kenya	11/133	8.3	4.7 – 14.2 %
Uganda	1/133	0.8	0.0 – 4.1 %
Pooled[1]	27/532	5.1	3.5 – 7.3 %

Table S2. Site-Specific Dose-Limiting Toxicities

[1]Meta-analysis random effects pooled estimate (using a generalized linear mixed model) is 4.5% with confidence interval of 2.3 – 8.8%.

	Screening Phase		Treatment Phase	
	Events	Participants	Events	Participants
Serious Adverse Events (total)	12	12	65	58
Vaso-Occlusive Pain/Dactylitis	2	2	6	6
Acute Chest Syndrome/Pneumonia	0	0	8	8
Acute Splenic Sequestration	1	1	8	7
Stroke	1	1	9	9
Severe anemia	0	0	7	7
Other Sickle-Related	0	0	1	1
Sudden Death, cause unknown	0	0	2	2
Malaria	2	2	10	10
Sepsis	3	3	9	9
Other Infection	2	2	3	3
Fever NOS	1	1	1	1
Other (Injury)	0	0	1	1

Table S3. Serious Adverse Events

Site	Sex	Age (Years)	Study Month	Cause of Death
Deaths in Screening				
02	Male	5	Screening	Sepsis
03	Male	8	Screening	Malaria
04	Male	3	Screening	Sepsis
04	Male	8	Screening	Sepsis
Deaths after Treatment Initiation				
01	Male	3	22	Sudden Death, cause unknown
01	Female	7	12	Sudden Death, cause unknown
01	Female	4	21	Severe Anemia
01	Female	9	3	Severe Anemia
01	Male	2	5	Suspected Sepsis
01	Male	9	12	Malaria
02	Female	2	10	Sepsis
02	Male	4	1	Malaria
02	Female	6	1	Malaria
02	Female	6	18	Malaria
02	Male	5	38	Pneumonia
02	Male	5	30	Stroke
03	Male	6	11	Septicemia
03	Male	3	11	Suspected Bacterial Infection
03	Female	6	33	Suspected Bacterial Infection
04	Female	7	16	Malaria

Table S4. Causes of Death